

Evidence for Pseudodominant Inheritance of Atrichia with Papular Lesions

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Abstract

Atrichia with papular lesions is a rare form of total alopecia, in which mutations in the *hairless* gene have been shown to underlie the phenotype. In the literature to date, atrichia with papular lesions has generally been reported to be inherited in an autosomal recessive manner. A few rare cases exist, however, in which parent-to-child transmission of atrichia with papular lesions has been documented. In this study, further investigations were carried out into the molecular basis of atrichia with papular lesions in a family with mother-to-son transmission by searching for mutations in the human *hairless* gene. Specifically, we wanted to determine whether this case truly represented an example of dominantly inherited atrichia with papular lesions, or whether another mode of inheritance might be responsible for the disorder in this kindred. Pseudodominant inheritance, for example, occurs when an individual with a known recessive disorder has a clinically unaffected partner, but then unexpectedly gives birth to children who are affected with the same recessive disorder as the affected parent, and can easily be distinguished from classical dominant inheritance with molecular diagnosis and haplotype analysis. In the family reported here, we have determined that both the mother and son are, in fact, homozygous for a novel mutation in the *hairless* gene, R33X. We provide the first evidence for pseudodominant inheritance in atrichia with papular lesions, and at the same time extend our knowledge of pathogenetic mutations in the human *hairless* gene. Importantly, this information allows revisions in genetic counseling for risk of transmission for individuals in the family, previously impossible in the absence of knowing the genetic basis of atrichia with papular lesions in this unusual kindred.

Keywords: hairless gene, mutation, papular atrichia, pseudodominant inheritance

Atrichia with papular lesions (APL) (OMIM 209500) is a rare form of irreversible alopecia that is inherited in an autosomal recessive pattern (Fredrich, 1950; Damste and Prakken, 1954; Lowenthal and Prakken, 1961). In affected individuals, hairs are typically absent from the scalp, axilla, and body, and patients are almost completely devoid of eyebrows and eyelashes. Histologic examination of affected scalp skin shows the complete absence of mature hair follicle structures. Normal hairs are present at birth in most APL patients, but these neonatal hairs are usually shed within the first few months of life and are never replaced. At approximately 2 y of age, APL patients begin to develop multiple follicular papules, and variations in the structure and morphology of the hair follicle remnants have been reported (Fredrich, 1950; Damste and Prakken, 1954; Lowenthal and Prakken, 1961; Kanzler and Rasmussen, 1986; Sinclair and DeBerker, 1997). Histologic studies in mice have revealed normal development of the hair follicle infundibulum and sebaceous gland, but severe malformation of the bulb region leading to the lack of new hair development, follicular degeneration, and the formation of deep dermal cysts with a thin lining of stratified squamous epithelium filled with laminated cornified cells (Panteleyev *et al*, 1998a,b,1999,2000). The combination of the clinical history of hair that was shed and never regrew, together with the development of papules with typical histology, is virtually pathognomonic for APL, and allows accurate discrimination between APL and other forms of total alopecia (Zlotogorski *et al*, 2001).

Recently, several authors have reported linkage of APL to chromosome 8p12 (Ahmad *et al*, 1998; Nothen *et al*, 1998; Sprecher *et al*, 1998) and then elucidated the genetic basis for this disorder by identifying mutations in the human *hairless*(*HR*) gene, which localizes to the same region of chromosome 8 (Ahmad *et al*, 1998). Subsequently, several additional mutations have been identified in families from around the world showing a similar phenotype, thereby establishing the molecular basis of this disorder (Cichon *et al*, 1998; Zlotogorski *et al*, 1998,2001; Ahmad *et al*, 1999a,b; Kruse *et al*, 1999; Sprecher *et al*, 1999a, b; Aita *et al*, 2000). In all cases in which mutations have been identified, there was evidence of consanguinity in the family, and all affected patients were found to be homozygous for the given mutation.

In the literature up to now, APL has generally been reported to be inherited in an autosomal recessive manner; however, two exceptional cases exist in which parent-to-child transmission of APL has been documented. The first case, reported by Kanzler and Rasmussen (1986), was present in a father and son. The second case in a mother and son, while not published as a separate report appears in Sinclair and DeBerker (1997, p. 165, fig 6.8c). This same case had been previously

presented in poster form at the Annual Meeting of the American Academy of Dermatology in 1992, and at the Royal Society of Medicine meeting in London, December 1993 (by R.S.).

In this study, we investigated the molecular basis of APL in this family by searching for mutations in the human *HR* gene. Specifically, we wanted to determine whether this case truly represented the first example of dominantly inherited APL, or whether an unexpected pattern of inheritance might be responsible for the disorder in this kindred.

Materials and methods

Human subjects

A family of Mediterranean origin with a mother and son affected with congenital atrichia was studied (**Figure 1**). The affected mother (II-2) and the unaffected father originated from the same small village; however, no clear history of consanguinity was elicited. We obtained DNA from the two affected individuals, and the mother's unaffected sister. Genomic DNA was isolated from peripheral blood collected in ethylenediamine tetraacetic acid (EDTA)-containing tubes according to standard techniques (Sambrook *et al*, 1989). All samples were collected following informed consent.

Mutation analysis

To screen for a mutation in the human *HR* gene, all exons and splice junctions were polymerase chain reaction (PCR) amplified from genomic DNA and sequenced directly in an ABI Prism 310 Automated Sequencer, using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit (PE Applied Biosystems, Foster City, CA), following purification in a Centriflex Gel Filtration Cartridges (Edge Biosystems, Gaithersburg, MD) as described earlier (Ahmad *et al*, 1999a). The mutation was identified by visual inspection and comparison with control sequences generated from unrelated, unaffected individuals. The mutation eliminates a recognition site for the enzyme *Xho*I, and was verified in the proband and his mother by restriction endonuclease digestion with this enzyme.

Microsatellite analysis

Microsatellite markers on chromosome 8 in the region of the *HR* gene were chosen from the genetic map at the Center for Medical Genetics, Marshfield Medical Research Foundation (Broman *et al*, 1998; <http://www.research.marshfieldclinic.org/genetics/>). Polymerase chain reaction primers for these markers were designed according to the sequences on the Genome Database

(<http://www.gdb.org>) and the Cooperative Human Linkage Center

(<http://www.lpg.nci.nih.gov/CHLC>). Polymerase chain reaction reactions were performed as follows: 3 min at 94°C, followed by 35 cycles of 30 s at 94°C, 30 s at 55°C, and 30 s at 72°C, and a final extension step of 5 min at 72°C. Polymerase chain reaction products were resolved on 6% nondenaturing polyacrylamide gels and visualized by ethidium bromide staining and genotypes were assigned by visual inspection.

Results

Clinical findings

Individual III-1

The patient is a 33 y old affected male, the son of individual II-2, who was born with short hair that fell out at approximately 40 d of age. Only a few hairs remained on the posterior and central part of the scalp, and these finally were shed at the age of approximately 10 y. Papules began to appear around the elbow at about the age of 15, and increased in number over time. He also suffers from photosensitivity. Physical examination revealed a total absence of scalp (**Figure 1b**) and body hair, with the exception of one to two eyebrow hairs and three to four lashes on the upper eyelids. His scalp was covered with tiny papules. Small papules were found over the posterior neck, shoulders, upper back, chest, and thighs. One papule was noted above the left eyebrow and none were found under the mid-line of the eye. A total of approximately 20 papules and cysts were present mainly around each elbow and a few (approximately seven) on each knee. Pitting was noted where lesions had regressed, with one pit on the elbow and two on the right knee. He had prominent facial erythema (atrophyderma vermiculatum) (**Figure 1d**) and some redness on the dorsal aspects of the hands. His scalp showed some whitish hypopigmented streaks associated with APL (Zlotogorski *et al*, 2001). He has normal nails, teeth, and sweating, as well as normal development and intelligence.

Individual II-2

The patient is a 65 y old affected female who was born with only scant hair that was soon shed. Papules began to appear around the elbow at about 20 y old, and the number increased with time. Interestingly, some of the lesions on the upper arms and on the knees regressed over time. She suffers from photosensitivity and facial redness, which improved with time. Physical examination revealed the total absence of scalp and body hair, with the exception of one to two eyebrow hairs. There was only one cyst on the scalp, and no papules present on the scalp, neck, chest, or back. A total of approximately 40 papules and cysts were present mainly around each elbow (**Figure 1a**) and on both arms. Pitting was noted mainly on the knee where lesions had regressed (**Figure 1c**).

She had mild facial erythema and some redness on the dorsal aspects of the hands. She has normal nails, teeth, and sweating, and normal development and intelligence.

Histopathology

Elbow

Biopsy of a large cyst on the elbow showed a thickened and uneven stratified epithelium (**Figure 2a**), notable for the presence of both pilar and epidermal characteristics. The granular layer (always present in epidermoid cysts and absent in pilar cysts) is present in some portions of cystic epithelium and absent in others (**Figure 2b**). The keratinous content of cyst is eosinophilic (more common for pilar cysts), but perfectly laminated (a feature of epidermoid cysts). The cells of cystic epithelium are gradually flattening as in most epidermoid cysts.

Scalp

No normal hair follicles are present. The remnants are represented only by their upper portions (infundibulum and sebaceous gland) (**Figure 2c**). The hair canal is prominently dilated and is filled with a mixture of sebum (sebaceous glands are normal) and corny material, a product of desquamation of the hair canal epithelium (**Figure 2d**). There is a prominent perifollicular lymphocytic infiltration just above the sebaceous gland. The absent lower portion of the hair follicle is replaced with fibrous tissue (**Figure 2e**). These features are very similar to scarring alopecia - lymphocytic infiltration of the upper portion of follicular sheath and consequent replacement of the entire follicle with fibrous tissue.

Identification of a mutation in the *HR* gene

We identified a homozygous C-to-T transition at nucleotide 97 in the *HR* gene leading to the conversion of an arginine residue (CGA) to a non-sense mutation (TGA) (**Figure 3a**). This mutation, designated R33X, abolishes a restriction endonuclease site for the enzyme *Xho*I, which was used as a screening assay in 34 chromosomes of unrelated unaffected individuals. The mutation was not found in the control DNA, suggesting that this nonsense mutation is not a polymorphism (**Figure 3b**). It is predicted that this nonsense mutation will lead to a complete absence of functional protein due to nonsense-mediated mRNA decay (Maquat, 1996; Frischmeyer and Dietz, 1999).

Exclusion of uniparental disomy using microsatellite markers

In order to discriminate between the possibilities of chromosome 8 uniparental disomy *vs* pseudodominant inheritance, we performed microsatellite analysis using markers

surrounding the *HR* gene on both affected individuals and the mother's unaffected sister (**Figure 3c**). It was immediately clear that the affected son had inherited one maternal chromosome and one chromosome clearly not present in the mother, presumably paternal. The unaffected sister appeared to share no common alleles in the region of the *HR* gene with the affected sister, although some markers were not fully informative. Furthermore, the affected mother and son shared the same haplotype for five markers over an 8.5 cM region (D8S258—D8S1771) surrounding the *HR* gene.

Discussion

Evidence is presented here for the first example of pseudodominant inheritance in APL in a mother and son of Mediterranean origin. Pseudodominant inheritance occurs when an individual with a known recessive disorder has a clinically unaffected partner, but then unexpectedly gives birth to children who are affected with the same recessive disorder as the affected parent (Thompson and Thompson, 1986). This pattern of inheritance mimics the appearance of a rare dominant trait in pedigrees. In contrast to a classical dominant pedigree, in a pseudodominant pedigree the trait will usually appear only in the parent sibship and their offspring, and nowhere else in the kindred. Consanguinity may or may not be present in the parents or in one set of grandparents. In recent years, evidence of pseudodominant inheritance has been demonstrated in a variety of disorders, including Stargardt disease, an inherited macular dystrophy, familial Mediterranean fever, nonsyndromic deafness (*DFNB1*), and Friedreich's ataxia, among other (Lewis *et al*, 1999;Booth *et al*, 2000;Illarioshkin *et al*, 2000;Pampanos *et al*, 2000;Shroyer *et al*, 2000).

Pseudodominant inheritance can easily be distinguished from dominant inheritance with molecular diagnosis and haplotype analysis. Usually, the unaffected partner is an unsuspecting carrier of a mutation in the same gene as the affected partner, and if consanguinity exists, frequently carries the identical mutation. In the family reported here, we have determined that both the mother (II-2) and son (III-1) are, in fact, homozygous for a novel mutation in the *HR* gene, R33X, thereby demonstrating evidence for pseudodominant inheritance in APL, and extending our knowledge of pathogenetic mutations in the human *HR* gene.

Important considerations in investigating the other possibilities that could generate this inheritance pattern would include loss of heterozygosity (and subsequent hemizyosity in the proband) in the region of the *HR* gene, or uniparental disomy of the maternal mutant chromosome. There are reports of both complete maternal and paternal uniparental isodisomy of chromosome 8 in probands with rare recessive disorders (Benlian *et al*, 1996) and even with normal appearance, stature, and intelligence, with one report of an ileal carcinoid tumor (Karanjawala *et al*, 2000). In one case, chromosome 8 uniparental disomy presents with neurologic impairment (Piantanida *et al*, 1997);

however, the remainder are associated with normal development. These findings suggest that no imprinted genes exist on human chromosome 8, and that uniparental disomy is tolerated and can lead to the appearance of recessive disorders. Further, loss of heterozygosity of chromosome 8 has been documented, however, largely in the context of different cancers (Brown *et al*, 1999; Ono *et al*, 1999; Seitz *et al*, 2000; Oba *et al*, 2001; Ryuet *et al*, 2001).

To rule out these possibilities, we performed haplotype analysis in the nuclear family with a large number of markers flanking the *HR* gene on chromosome 8, and with markers spanning the entire chromosome. We found that the unaffected sister (II-1) shares neither chromosome 8 haplotype in the region of the *HR* gene with the affected sister (II-2), consistent with the observation that she does not carry the mutation R33X; however, both the mother (II-2) and affected son (III-1) are homozygous for a series of markers flanking the *HR* gene, over a region of approximately 8.5 cM (**Figure 3c**). The son carries alleles of several markers that are not found in the maternal chromosome (left haplotype of III-1). This suggests the presence of a paternal chromosome (right haplotype of III-1) and argues against the possibility of disomy of the maternal chromosome because, with the exception of a few noninformative markers, there is evidence for two alleles in the son over the entire chromosome. While unlikely, there is still the remote possibility of loss of heterozygosity in the 8.5 cM region of homozygosity in the son, though the rest of the chromosome appears intact. Although the family denies any known history of consanguinity, the presence of a shared haplotype on both alleles of the mother and son, together with the origin of the parents from the same small village, suggest some relationship between II-2 and the father of III-1.

Molecular diagnosis will have a profound effect on individual III-1 in this family. Up to now, this individual had been counseled that he had inherited a "dominant" disorder, and that his risk of transmission to his children would be 50% to each offspring. He currently has one unaffected daughter, and his partner is not a carrier of this mutation, R33X (data not shown). Now that we have demonstrated that he has actually inherited APL in a pseudodominant manner, however, and shown that he is homozygous for a recessive mutation, his risk of transmission can be revised accordingly. Instead of 50%, his risk of having an affected child is now as low as the general population, provided that his wife is not also a carrier of an *HR* gene mutation other than R33X. All of his children will be carriers of the mutation R33X, but none of them should be affected in the absence of any further unusual modes of inheritance in this family.

The clinical, histologic, and genetic picture of APL in this family is similar to previous reports, including atrichia prior to the age 1 y, associated papules and cysts, absence of normal hair follicle structures, follicular cysts and mutation(s) in the *HR* gene (summarized in Zlotogorski *et al*, 2001);

however, in this family, there are some interfamilial and intrafamilial variations that are worth noting. Specifically, the mother had a more severe clinical picture with regard to the number of papules and cysts surrounding the elbows associated with regressed lesions around the knees, and less erythematous involvement of the face. Both members of the family had a more pronounced involvement of the large elbow lesions, and an atrophodermic erythematous appearance of the face that was previously seen only in a few of our APL patients. Biopsies taken from the son also showed lymphocytic involvement in the upper portion of the follicle and an associated epidermoid component of the elbow cyst. Similar to those reported by Nomura *et al* (2001), the cysts in this family were noteworthy in that if the origin of the cyst is from the infundibulum, the result is an epidermoid cysts, whereas if the origin of the cyst is from the isthmus, the result is a pilar cyst. Collectively, these findings suggest that APL is a dynamic disease process, and that modifying genes may be involved in determining the final clinical picture. Therefore, it is important to increase our clinical, histologic, and genetic knowledge about the nature of this disease by repeated examination of many patients and many families over time. As in this kindred, such information will lead to improvements in genetic counseling and accurate clinical diagnosis and treatment of APL in affected families, particularly in those with unusual modes of inheritance.

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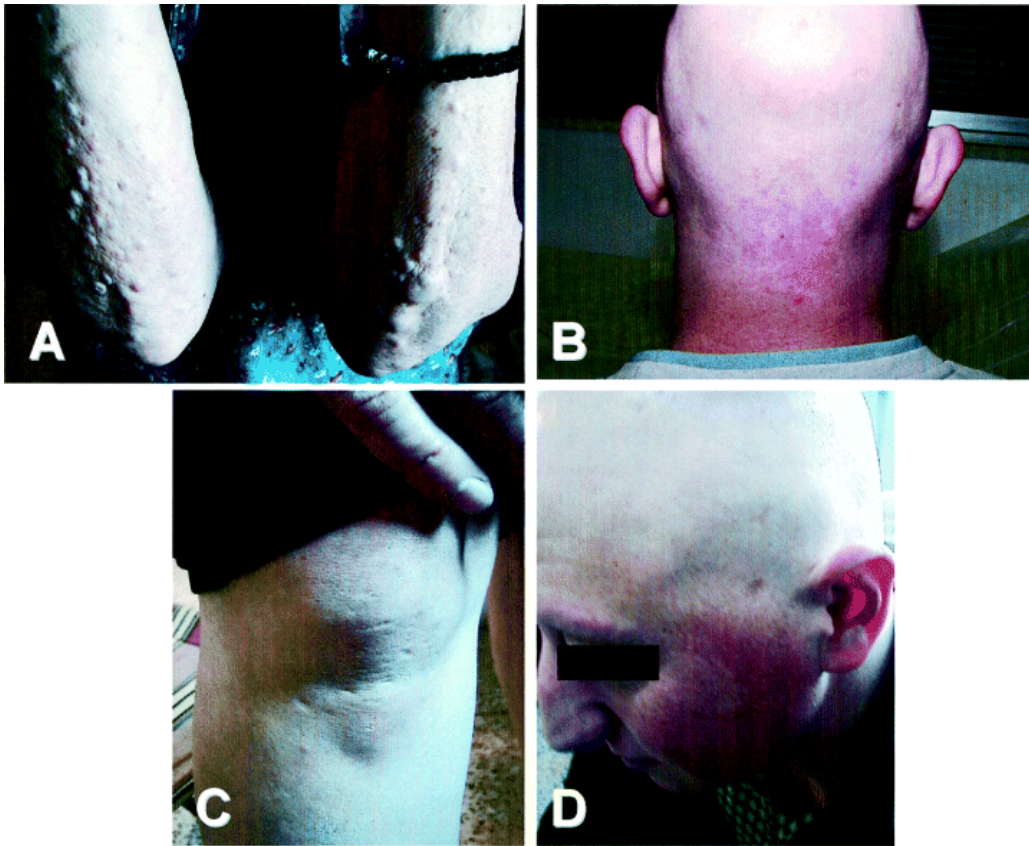
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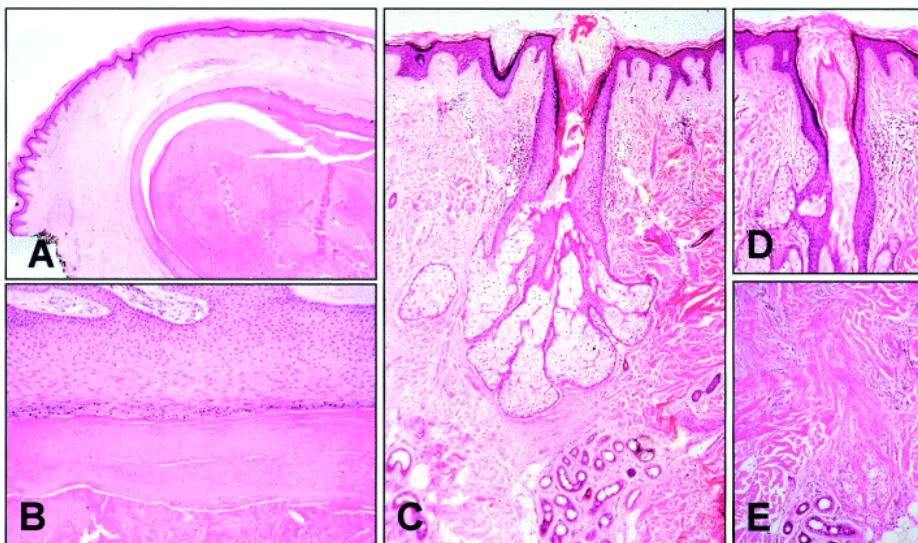
Figures

Figure I

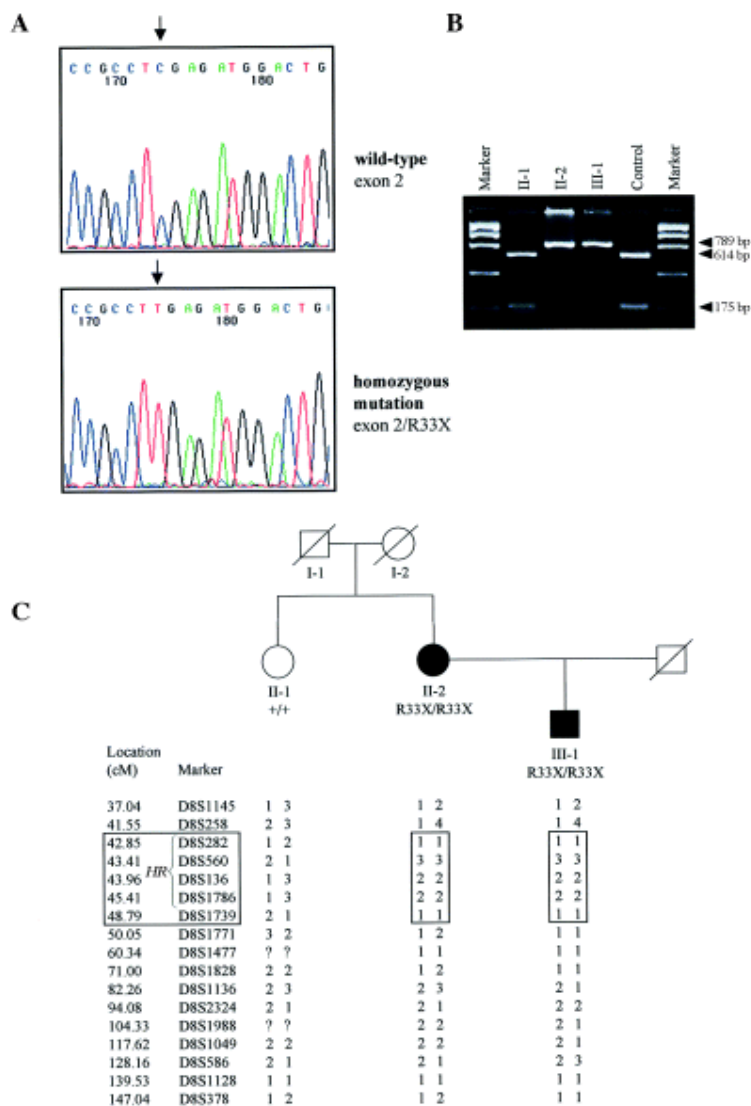


Clinical presentation of APL in individuals III-1 and II-2. (A) Note the multiple papules and cysts on arms and elbows of individual II-2. (B) Complete scalp atrichia in individual III-1. Note the hypopigmented marks. (C) Pitting on the knee due to regressed papular lesions in individual II-2. (D) Total lack of scalp and eyebrow hair, and atrophoderma vermiculatum of the cheek in individual III-1.

Figure II



Histology of the scalp and elbow from individual III-1. Elbow: The epidermis is essentially normal. Note the presence of a large cyst with a thickened and uneven stratified epithelium (A), notable for the presence of both pilar and epidermal characteristics. The granular layer (always present in epidermoid cysts and absent in pilar cysts) has a patchy pattern - it is present in some portions of cystic epithelium and absent in others (B). The keratinous content of cyst is eosinophilic (more common for pilar cysts) but perfectly laminated (a feature of epidermoid cysts). The cells of cystic epithelium are gradually flattening as in most epidermoid cysts. Scalp: No normal hair follicles are present. The remnants are represented only by their upper portions (infundibulum and sebaceous gland) (C). The hair canal is prominently dilated and is filled with a mixture of sebum (sebaceous glands are normal) and corny material, a product of desquamation of the hair canal epithelium (D). There is a prominent perifollicular lymphocytic infiltration just above the sebaceous gland. The absent lower portion of the hair follicle is replaced with fibrous tissue (E). The sweat gland and its canal are normal.



Molecular analysis of the hairless (HR) gene in the family. (A) Sequence analysis reveals a homozygous mutation in the two affected individuals. The wild-type sequence is shown in the upper panel for comparison, and the arrow indicates the CGA codon for arginine at nucleotide 97 of the hairless mRNA. The lower panel shows a homozygous mutation at this position, and the arrow indicates the C-to-T transition to TGA, generating a nonsense mutation, designated R33X. (B) The mutation was verified by restriction digestion with the endonuclease XhoI. The mutation R33X abolishes a restriction site, thus, the control individual and the unaffected older sister (II-1) display only the digested fragments (614 + 175 bp) from the 789 bp polymerase chain reaction product. The presence of the mutation is shown in the two affected individuals II-2 and III-1 by the lack of cleavage of the 789 bp fragment by XhoI, as the site was destroyed by the mutation. (C). Haplotype analysis of three members of the nuclear family. The unaffected sister (II-1) shares neither chromosome 8 haplotype with the affected sister (II-2) in the region of the HR gene, consistent with the observation that she does not carry the mutation R33X, although in the case of certain markers, phase could not be assigned. Both the mother (II-2) and affected son (III-1) are homozygous for a series of markers flanking the HR gene, over a region of approximately 8.5 cM (boxed markers). The son carries alleles of several markers that are not found in the maternal chromosome (left haplotype of III-1). Phase for markers D851145 and D85258 could not be assigned. This suggests the presence of a paternal chromosome (right haplotype of III-1) and argues against the possibility of uniparental disomy of the maternal chromosome or extensive loss of heterozygosity.